PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	A Study Protocol of a Multicentre double blind RCT, comparing a traditional RCT with an aggregated N-of-1 trial: GAG-therapy Efficacy Trial Solution for Bladder pain syndrome/ Interstitial Cystitis (GETSBI study).
AUTHORS	van Ginkel, Charlotte; Baars, Cléo; Heesakkers, John; Martens, Frank; Janssen, Dick

VERSION 1 – REVIEW

REVIEWER	Saleh, Omar University of Florence
REVIEW RETURNED	27-Nov-2022

GENERAL COMMENTS	The work is very interesting especially for the methodology used. Despite everything I have complaints 1 In the exclusion criteria - you write "pain..due anyother couses". what did you investigated and how (former tumor pathologies, autoimmune neurological parts) - was age considered an inclusion criterion? - you have excluded bladder instillation of Botulinum, did you excluded previous instillations of intravesical CHT as well? 2 You write in the paragraph methods and analysis "on cystoscopy several parameters are routinaly evaluatted" which ones? what influence do they have in your analysis? explain in detail. 3 Was hydrodistension performed during the cystoscopy? Was Cystoscopy performed tunder anesthesia? 4 Your study always differ from the previous ones in the literature by several factors including the fact that it does not distinguish between inflammatory and non-inflammatory pathology (First paragraph of Discusion). Have you performed biopsy during cystoscopy? explain in detail 5 Since it is a rare pathology, why not include other types of patients other than patients with Hunner lesion and then apply the same method after stratification. Explain the reasons beyond those set out in discussion from line 3 6 What results did the methodology used? The results must be published together with the methodology as although the efficacy of the therapy has already been highlighted, the efficacy of the

	treatment must be well explained also in this work and well detailed by eliminating all possible bias, especially given the statistical strategy to obtain a level evidence 1

REVIEWER	Gülpınar, Ömer Ankara University
REVIEW RETURNED	06-Dec-2022

GENERAL COMMENTS	This is a well designed double-blind multi-design multi-centre randomized placebo-controlled study protocol to assess the short and long-term efficacy of Hyaluronic acid (1.6%) + Chondroitin sulfate (2%) therapy (Ialuril ® Prefill, IBSA, Goodlife) in symptomatic BPS/IC patients with Hunner lesions. I have a few recommendations for the authors 1-Are the questionnaires to be used in the study validated in your language? These should be stated 2- Pathological examination should be performed to exclude other possible pathologies other than Hunner's ulcer 3- 3-day bladder diary parameters before and after treatment should also be added to secondary endpoint of the study

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Omar Saleh, University of Florence
Comments to the Author:
The work is very interesting especially for the methodology used.
• Thank you for your response and thorough excellent reviewing, below we have tried to answer to your questions/suggestions as careful as possible.

Despite everything I have complaints

1 In the exclusion criteria
- you write "pain..due anyother couses". what did you investigated and how (former tumor pathologies, autoimmune neurological parts)
• This is based on patients medical history and interview, we have added this information in table 1 (page 9).
- was age considered an inclusion criterion?
• Yes, adult patients > 18 year with symptomatic BPS/IC HL+ with VAS ≥ 4 are included. We have added this in the text (page 6) and in table 1 (page 9).
- you have excluded bladder instillation of Botulinum, did you excluded previous instillations of intravesical CHT as well?
• The diagnosis of BPS/IC means excluding other causes (such as malignancy), hereby instillations of intravesical CHT is excluded as well.

2 You write in the paragraph methods and analysis "on cystoscopy several parameters are routinaly evaluatted" which ones? what influence do they have in your analysis? explain in detail.
• The cystoscopy parameters that are evaluated are: number of Hunner Lesions, estimated % of inflammation of bladder wall (VAS scale 0-100%) and overall assessment of degree of bladder inflammation (5 point Likert scale). They are measured at time points: week 0, week 8 and week 28. The cystoscopy parameters are secondary outcome measurements, where the 1) change in estimated percentage of inflammation of the bladder wall (area covered by HL) and 2) change in grade of inflammation will be independently evaluated. Moreover, also the correlations between these two secondary outcomes measurements will be investigated.

This information has been added in the text (page 7).

3 Was hydrodistension performed during the cystoscopy? Was Cystoscopy performed under anesthesia?
4 Your study always differ from the previous ones in the literature by several factors including the fact that it does not distinguish between inflammatory and non-inflammatory pathology (First paragraph of Discusion). Have you performed biopsy during cystoscopy? explain in detail
• The answer below is for question 3 and 4.

All patients included in the study have received a cystoscopy and had typical Hunner lesions confirmed even without hydrodistension. All other pathologies (CIS) were excluded (because this is an criteria for diagnosis of BPS/IC) so these are all inflammatory. Hydrodistension and biopsy were not routinely performed due to the fact that hydrodistension and biopsy causes damage and affects the primary outcome measurement pain.

5 Since it is a rare pathology, why not include other types of patients other than patients with Hunner lesion and then apply the same method after stratification. Explain the reasons beyond those set out in discussion from line 3
• The inclusion criteria of Hunner Lesions was a requirement of the Dutch government (this study is in collaboration with the Dutch government (Zorginstituut Nederland)), to have an objective measurement within the study. Glomerulations are less disease specific.
We are currently discussing with the government to possibly start a parallel study (non-inferiority set up) for the BPS/IC Type 1 and 2.

6 What results did the methodology used? The results must be published together with the methodology as although the efficacy of the therapy has already been highlighted, the efficacy of the treatment must be well explained also in this work and well detailed by eliminating all possible bias, especially given the statistical strategy to obtain a level evidence 1
• The primary methodology in the study is the RCT. This study can validate the design of single cross-over and aggregated N-of-1 trial, by actively comparing/evaluating the outcome measurements in the study.
The study is double blind with appropriate wash-out periods between treatment periods to minimize possible wash-over bias.
The study models will be compared on significance level and correlation level. The primary and secondary outcome measurements will be evaluated in average changes (with standard deviation) between the models.
This explanation has been added at page 11.

Reviewer: 2
Dr. Ömer Gülpınar, Ankara University
Comments to the Author:
This is a well designed double-blind multi-design multi-centre randomized placebo-controlled study protocol to assess the short and long-term efficacy of Hyaluronic acid (1.6%) + Chondroitin sulfate (2%) therapy (Ialuril ® Prefill, IBSA, Goodlife) in symptomatic BPS/IC patients with Hunner lesions.
• Thank you for your excellent reviewing and your recommendations. We have tried to response as careful and completely as possible.

I have a few recommendations for the authors 1-Are the questionnaires to be used in the study validated in your language? These should be stated
• This is the case, we have added this statement on page 7.

2- Pathological examination should be performed to exclude other possible pathologies other than Hunner's ulcer
• This topic did arise also for reviewer 1, hence there is some repetition in our response. All patients included in the study have received a cystoscopy and had typical Hunner Lesions confirmed even without hydrodistension. All other pathologies (CIS) were excluded (because this is a criteria for diagnosis of BPS/IC). Hydrodistension and biopsy were not routinely performed due to the fact that both cause damage and affects the primary outcome measurement pain.
When the urologist doubts between a Hunner Lesions and CIS, a biopsy is indicated and patient is not eligible for the study, because the diagnosis BPS/IC with HL is not established. Afterwards, in

case of no malignancy exclusion criteria 5 will be enforced.

3- 3-day bladder diary parameters before and after treatment should also be added to secondary endpoint of the study
• Two-day bladder diary is assessed and added as secondary endpoint.

VERSION 2 – REVIEW

REVIEWER	Saleh, Omar University of Florence
REVIEW RETURNED	17-Jan-2023

GENERAL COMMENTS	RE1 You have excluded bladder instillation of Botulinum, did you excluded previous instillations of intravesical CHT as well? RE Authors The diagnosis of BPS/IC means excluding other causes (such as malignancy), hereby instillations of intravesical CHT is excluded as well. RE 2 I would explain it better and more clearly in the text RE 1 Was hydrodistension performed during the cystoscopy? Was Cystoscopy performed tunder anesthesia? Your study always differ from the previous ones in the literature by several factors including the fact that it does not distinguish between inflammatory and non-inflammatory pathology (First paragraph of Discusion). Have you performed biopsy during cystoscopy? explain in detail RE Authors All patients included in the study have received a cystoscopy and had typical Hunner lesions confirmed even without hydrodistension. All other pathologies (CIS) were excluded (because this is an criteria for diagnosis of BPS/IC) so these are all inflammatory. Hydrodistension and biopsy were not routinely performed due to the fact that hydrodistension and biopsy causes damage and affects the primary outcome measurement pain. RE 2 There are different levels of diagnosis of BPS/IC. All patients have undergone before protocol's inclusion to bladder lesion biopsy and/or bladder biopsy? Please explain

REVIEWER	Gülpınar, Ömer Ankara University
REVIEW RETURNED	23-Jan-2023

GENERAL COMMENTS	I just had one little criticism; I couldn't see the reference for the O'Leary Sant Interstitial Cystitis Symptom and Problem scales. If you applied these scales in Dutch, please refer to the validity and reliability analyzes of these scales in your language, since, it must be validated and reliable in the language it is translated into.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Dr. Omar Saleh, University of Florence

Comments to the Author:
RE1 You have excluded bladder instillation of Botulinum, did you excluded previous instillations of intravesical CHT as well?
RE Authors The diagnosis of BPS/IC means excluding other causes (such as malignancy), hereby instillations of intravesical CHT is excluded as well.
RE 2 I would explain it better and more clearly in the text
We have tried to explain this more clearly in the section 'Methods and Analysis'. We extended inclusion criteria 1 to: 1) pain, discomfort in pelvic region of inflammatory bladder conditions due to any other causes based on patients' medical history and interview (i.e. bladder pathologies and instillations with irritative agents, such as intravesical chemotherapy). There are exceptions for irritable bowel syndrome, hypertonic pelvic floor and urinary tract infections fewer than 3 per year. These are noted by ESSIC as a confusable diseases. see page 6.

RE 1
Was hydrodistension performed during the cystoscopy? Was Cystoscopy performed tunder anesthesia?
Your study always differ from the previous ones in the literature by several factors including the fact that it does not distinguish between inflammatory and non-inflammatory pathology (First paragraph of Discussion). Have you performed biopsy during cystoscopy? explain in detail
RE Authors All patients included in the study have received a cystoscopy and had typical Hunner lesions confirmed even without hydrodistension. All other pathologies (CIS) were excluded (because this is an criteria for diagnosis of BPS/IC) so these are all inflammatory. Hydrodistension and biopsy were not routinely performed due to the fact that hydrodistension and biopsy causes damage and affects the primary outcome measurement pain.
RE 2 There are different levels of diagnosis of BPS/IC. All patients have undergone before protocol's inclusion to bladder lesion biopsy and/or bladder biopsy? Please explain
For this study IC/BPS patients type 3 are included, type 3C is not mandatory, hence biopsies are not performed within the study protocol. But before protocol inclusion, in the work-up of IC/BPS in the Netherlands biopsies are routinely performed for the main reason excluding confusable diseases.

Reviewer: 2
Dr. Ömer Gülpınar, Ankara University

Comments to the Author:
I just had one little criticism;
I couldn't see the reference for the O'Leary Sant Interstitial Cystitis Symptom and Problem scales. If you applied these scales in Dutch, please refer to the validity and reliability analyzes of these scales in your language, since, it must be validated and reliable in the language it is translated into.
Thank you for addressing this again. The ICSI ICPI has been translated in Dutch and used in previous clinical trials. However, it has not been officially validated yet, so we need to reclaim our previous response. We misread the questions concerning our own language. We have changed this back on page 7 and added the sentence 'All questionnaires are in Dutch'.